CLAIMS

1. A method of generating a nucleoside library, comprising:

providing a first nucleoside and a second nucleoside, each having a first reactive group protected with a first protecting group and a second reactive group protected with a second protecting group, wherein the first and second nucleosides are coupled to a solid support;

removing the first protecting group from the first and second nucleosides and reacting the first reactive group of the first nucleoside with first reagent and the first reactive group of the second nucleoside with a second reagent; and

removing the second protection group from the first and second nucleosides and reacting the second reactive group of the first nucleoside with a third reagent and the second reactive group of the second nucleoside with a fourth reagent.

2. The method of claim 1 wherein the first and second reagents are chemically identical.

3. The method of claim 1 wherein the step of reacting the second reactive group of the first nucleoside with the third reagent and the second reactive group of the second nucleoside with the fourth reagent is performed in separate compartments.

4. The method of claim 1 wherein at least one of the first and second nucleosides is coupled to a solid support via a linker molecule.

5. The method of claim 4 wherein the coupling of the linker molecule to the nucleoside comprises an acetal bond.

5. The method of claim 1 wherein the first nucleoside and the second nucleoside are chemically distinct from each other.

6. The method of claim 1 wherein at least one of the first and second nucleosides comprises a ribofuranose and a natural nucleoside base.

7. The method of claim 1 wherein the solid support comprises a polystyrene resin or a polystyrene-polyethylene glycol copolymer.

8. The method of claim 1 wherein the first protecting group comprises a *p*-methoxy-benzyl group and the second protecting group comprises a benzyl group.

9. The method of claim 1 wherein at least one of the first, second, third, and fourth reagent comprises a nucleophile.

10. The method of claim 9 wherein at least one of the first, second, third, and fourth reagents are selected from the group consisting of a Grignard reagent, an organo-lithium reagent, and a Wittig reagent.

11. A method of generating a nucleoside library, comprising:

providing a first sugar and a second sugar, wherein each of the first and second sugars have at least one reactive group and are covalently bound to a solid support;

reacting the first and second reactive groups with a first heterocyclic base and a second heterocyclic base, respectively, thereby forming a first nucleoside and a second nucleoside; and

reacting the first and second nucleoside with a first and second reagent in at least one subsequent reaction, respectively, thereby forming a first modified nucleoside and a second modified nucleoside.

12. The method of claim 11 wherein the first and second sugars are chemically identical.

13. The method of claim 11 wherein the step of reacting the first and second nucleosides with a first and second reagent, respectively, is performed in separate compartments.

14. The method of claim 11 wherein at least one of the first and second sugars is coupled to a solid support via a linker molecule.

15. The method of claim 11 wherein the coupling of the linker molecule to the nucleoside comprises an acetal bond.

16. The method of claim 11 wherein the first and second heterocyclic bases are chemically distinct from each other.

17. The method of claim 11 wherein the heterocyclic base comprises a moiety selected from the group consisting of an imidazole, a thiazole, and an oxazole.

18. The method of claim 11 wherein at least one of the first and second sugars comprises a ribofuranose.

19. The method of claim 11 wherein the solid support comprises a polystyrene resin or a polystyrene-polyethylene glycol copolymer.

20. The method of claim 11 wherein the first and second modified nucleosides are formed in two subsequent reactions.

21. A method of generating a nucleoside library, comprising:

providing a first nucleoside and a second nucleoside, each having a reactive group and each being coupled to a solid support; and

reacting the reactive group of the first and second nucleoside with a first reagent and second reagent, respectively, thereby forming a first modified nucleoside and a second modified nucleoside, wherein the second modified nucleoside is chemically distinct from the first modified nucleoside.

22. The method of claim 21 wherein at least one of the first and second nucleosides comprises a purine heterocyclic base.

23. The method of claim 21 wherein each of the first and second nucleosides comprises a sugar moiety and a heterocyclic base, and wherein the reactive group is disposed on the heterocyclic base of the first and second nucleosides.

24. The method of claim 21 wherein each of the first and second nucleosides further comprises a second reactive group.

25. The method of claim 24 further comprising a step of reacting the second reactive group of the first and second nucleoside with a third reagent and a fourth reagent, respectively.

26. The method of claim 21 wherein the first and the second reagents are selected from the group consisting of an alkyl, an aryl, an alkynyl, an alcohol, and an amine.